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Review article

Electrical nerve stimulation for xerostomia: A meta-analysis of randomised controlled trials

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ABSTRACT

Background: Xerostomia leads to caries, infection and overall psychological discomfort. Salivary substitutes and pharmacological agents have been tried only with temporary relief. The use of transcutaneous electrical nerve stimulation (TENS) has been contemplated on by various researchers for treatment of xerostomia. We carried out the present review as a systematic compilation and quantitative synthesis of the existing evidence related to the utility of TENS in patients with xerostomia.
Methodology: Six randomized controlled trials were identified from databases for inclusion and analysed using non-Cochrane mode in RevMan 5.0 software. The heterogeneity between the studies were assessed using Forest plot, I^2 statistics wherein more than 50% was considered to have moderate to severe heterogeneity and Chi-square test with a statistical P-value of less than 0.10 to indicate statistical significance.
Results: Results show that the effect of TENS on salivary flow rate in 369 participants with SMD [95% CI] was 0.63 [-0.03, 1.29] and was not statistically significant.
Conclusion: To conclude, the current evidence does not support the use of TENS in patients with xerostomia and may be considered as a salivary substitute for symptomatic improvement. However the type, frequency and amplitude of current used needs to be studied in detail. High quality randomized controlled trials with adequate power are required, either to support or refute the use of TENS in xerostomia.

1. Introduction

TENS, an acronym for transcutaneous electrical nerve stimulation, is the use of electric current delivered via specific device for therapeutic purposes. It produces an electrical impulse which can be adjusted for pulse, frequency and intensity. In dentistry, this has been widely advocated for the treatment of oro-facial pain and temporomandibular joint disorders.[1,2] Though the use of TENS was majorly concentrated on pain, few clinical trials have been conducted to identify the effect of electrical nerve stimulation on salivary flow.[3] Xerostomia, also termed as dry mouth or dry mouth syndrome is combination of change in the composition of saliva with reduced salivary flow (hyposalivation).[3,4] It is one common problem estimated with a prevalence of 10–29% of the population, with a female predominance. Anti-cholinergic action of various drugs, radiotherapy of head and neck and diseases of the salivary gland like Sjogren's syndrome have been attributed to cause xerostomia. Treatment of xerostomia has been attempted with the use of lubricants and salivary substitutes which provide temporary and intermittent relief, with the recurrence of symptoms when the treatment is interrupted. Pilocarpine has been widely used but they are not without adverse effects.[4] With this in mind TENS was tried as an alternative treatment option due to its stimulatory effect on the salivary flow caused due to the release of endorphins in the opiate receptors.[2] The main advantage of using TENS is that it is non-invasive when compared to medications, which have their systemic side effects. A review on TENS for xerostomia has been reported by Fedele *et al.*[3] However it was not formulated in a systematic way and meta-analytic principles were not applied. Hence this systematic review and meta-analysis will aim to compile the available evidences on the utility of TENS for xerostomia.

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2. Method

2.1. Information sources and search strategy

The protocol for this review was registered with International prospective register of systematic reviews (PROSPERO) with the registration number CRD42016036259. The review protocol can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016036259. A thorough literature search was conducted and was completed on 21 March 2016. The primary data base used was Medline (via PubMed), Cochrane central register of clinical trials (CENTRAL) and Database of Abstracts of Reviews of Effects (DARE). The key words used were (nerve stimulation [tiab] OR electrical stimulation [tiab]) AND xerostomia [tiab]. This search was further supplemented by hand searching of relevant references from review articles and other eligible studies. No limits were applied to the year of study, but only studies published in English language were included for the review.

2.2. Eligibility criteria

Only those studies with randomized controlled design conducted on healthy participants or patients administered with TENS in any location for xerostomia due to any aetiology were considered for this review. The comparator group may either have received placebo or no intervention. The outcome measure was the improvement in the salivary flow between the interventions. Specific exclusion criteria were not set due to lack of available research in the field.

2.3. Study procedure

Both the authors independently screened the above mentioned data bases for studies and analysed abstracts for possible inclusion. Full-texts articles were obtained for those found to be eligible. A pre-tested data extraction form was created and both the authors independently extracted the following data from each eligible study: trial site, year, trial methods, participants, interventions, and outcomes. Disagreement between the authors was resolved through discussion. The extracted data were analysed using non-Cochrane mode in RevMan 5.3 software. The methodological quality of eligible trials was independently assessed using The Cochrane collaboration's tool for assessing the risk of bias. We followed the guidance to assess whether trials took adequate steps to reduce the risk of bias across six domains: sequence generation, allocation concealment, blinding (of participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias. The judgement was categorized into low, high or unclear risk of bias.[5] Standardized mean difference (SMD) with 95% confidence interval was used in the final Forest plot. The heterogeneity between the studies were assessed using the Forest plot visually, I^2 statistics wherein more than 50% was considered to have moderate to severe heterogeneity and Chi-square test with a statistical P-value of less than 0.10 to indicate statistical significance. Random-effect models were used in case of moderate to severe heterogeneity. The present meta-analysis was conducted and presented in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[6]

Table 1
Key details of the included studies in the systematic review.

Study	Participants	Intervention	Location, Frequency and Amplitude	Control	Outcome
Steller M 1988[7]	24 patients diagnosed with xerostomia due to Sjogren's syndrome	12 patients on TENS used for 3 min, 3 times a day for 4 weeks	Tongue and hard palate Frequency and amplitude were not mentioned	12 patients on Placebo device used for 3 min, 3 times a day for 4 weeks	Whole saliva flow rates measured at weeks 0,2 and 4 by collection of whole saliva before and after stimulation
Talal N 1991[8]	77 patients diagnosed with xerostomia due to Sjogren's syndrome	40 patients on TENS used for 3 min, 3 times a day for 4 weeks	Oral Mucosa Frequency and amplitude were not mentioned	37 patients on Placebo device used for 3 min, 3 times a day for 4 weeks	Whole saliva flow rates measured at weeks 0,2 and 4 by collection of whole saliva before and after stimulation
Strietzel FP 2011[9]	79 patients diagnosed with xerostomia due to Sjogren's syndrome	Stage I – 79 patients on electrostimulation used in the clinic for 10 min in for 1 month Stage II – 79 patients on electrostimulation for 9 months used at 1,5 or 10 min	Oral mucosa in the third molar region The frequency and amplitude were not mentioned	Stage I – 70 patients on mechanical and electrical stimulation administered in the clinic for 10 min for one-month	Resting and Stimulated salivary flow rate to analyse the cumulative effect of electrostimulation from Stage I and Stage II
Weiss 1986[10]	24 patients diagnosed with xerostomia	11 patients on TENS for 3 min administered 3 times for 3 weeks (1 stimulus per week)	Dorsum of the tongue The maximum voltage delivered was 6V. The frequency and amplitude was not clearly mentioned.	13 patients on placebo device administered similar to the active device	Subjective response by patient Clinicians assessment of salivary status on examination
Lakshman 2015[11]	30 patients diagnosed with xerostomia after undergoing radiotherapy for head and neck.	20 patients on TENS for 5 min during (10 patients) 3rd and 4th week of radiotherapy and after a month of completion of radiotherapy (10 patients).	Skin overlying the parotid gland The frequency was 500 Hz and amplitude was not mentioned.	10 healthy participants with no complain of dry mouth and not undergone radiotherapy.	Stimulated and unstimulated salivary flow rate within and between the groups
Strietzel FP 2007[12]	23 patients diagnosed with xerostomia	23 patients on electrostimulating device (active mode) for 10 min	Oral mucosa in the third molar region The frequency and amplitude were not mentioned	23 patients on electrostimulating device (sham mode) for 10 min Randomly alternating with active mode at an interval of 35 min.	Stimulated salivary flow rate

3. Results

3.1. Search results

A total of 18 articles were identified, of which 4 were obtained from title screening. Abstracts of these were reviewed to ensure that they met the inclusion criteria and 2 more studies were identified eligible on reference search. All these 6 studies were read in entirety to confirm eligibility. Table 1 shows the list of included studies.[7–13] The study flow chart according to PRISMA is shown in Fig. 1. Publication bias could not be checked as there were only six eligible studies for inclusion in this review. Summary of risk of bias of individual studies is depicted in Fig. 2.

3.2. Pooled results

3.2.1. Salivary flow rate

Except for one,[10] all other included studies assessed the effect of TENS on salivary flow rate in a total of 369 participants and the SMD [95% CI] was found to be 0.63 [-0.03, 1.29] and was not statistically significant. Fig. 3 depicts the Forest plot of salivary flow rate from the included studies.

3.2.2. Subjective improvement

Only one of the included studies[10] assessed symptomatic improvement with SMD [95% CI] of 1 [0.6, 1.66] and was not statistically significant.

4. Discussion

The present review is an attempt to identify the effect of electrical nerve stimulation on salivary flow in order to identify TENS as a possible treatment alternative for xerostomia. This is because the available treatment options provide only temporary relief of symptoms and recurrence is seen upon discontinuation. Also the pharmacological agents used for xerostomia have been associated with adverse effects.

Salivary production is a regulated mechanism of the autonomic nervous system, the parasympathetic nervous system producing abundant saliva and the sympathetic stimulation decreases their production. Xerostomia is a clinical condition wherein there is a decrease in the quantity of saliva produced with change in the composition. Various causes have been attributed to xerostomia including drugs, radiotherapy of head and neck and diseases like Sjogren's syndrome.[13] Xerostomia can lead to difficulty in speaking and swallowing. Lubrication, buffering and other protective functions of saliva are also compromised. This can lead to dental caries, infection and overall poor oral health and hygiene, which might all add up to a negative effect on the quality of life. Treating dentist also face problems because the condition is difficult to treat and interferes with other dental treatment outcomes. Treatment with salivary substitutes and lubricants provide temporary relief but cannot completely treat the condition. Pharmacological agents like Pilocarpine have been tried but they are limited due to the side effects caused.[14]

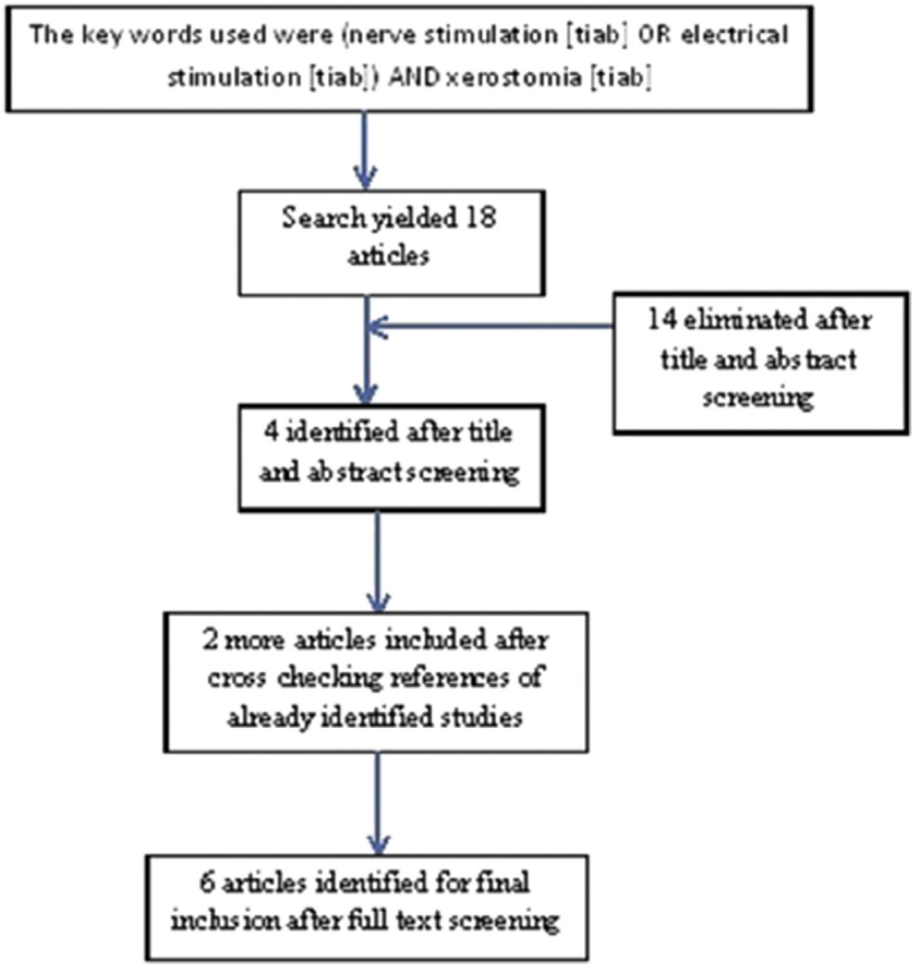

Fig. 1. Study flow chart.

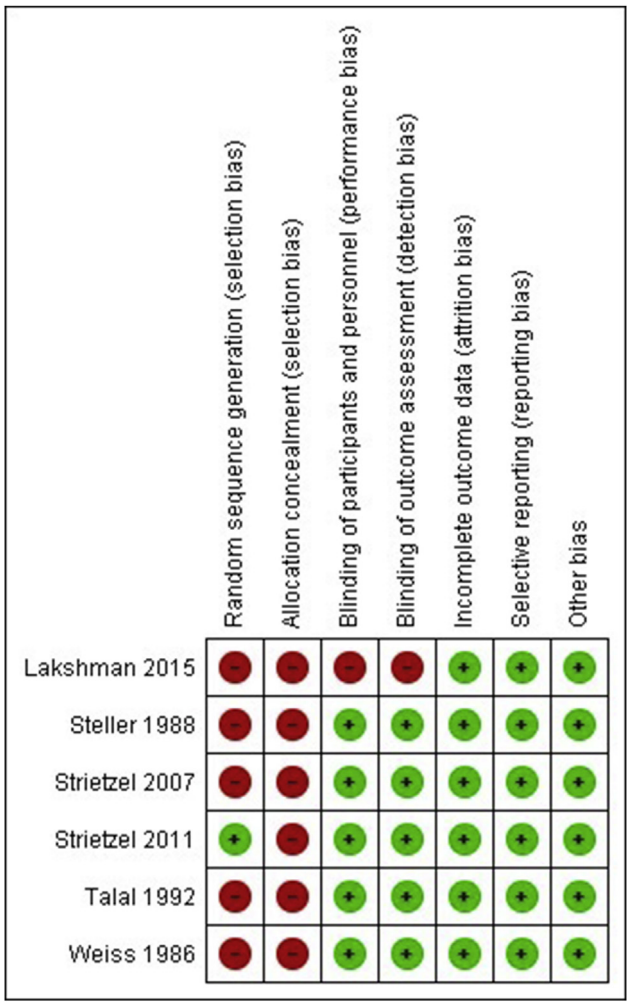

Fig. 2. Risk of bias of included studies as per Cochrane's tool.

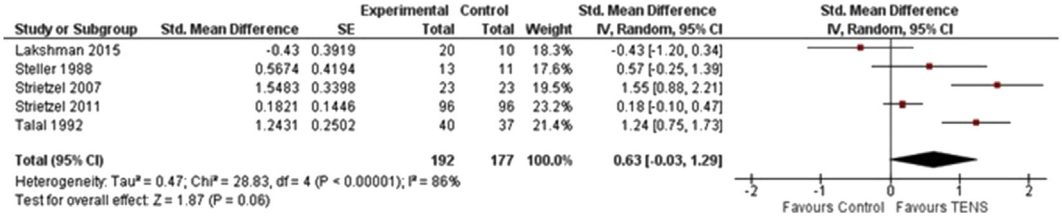

Fig. 3. Forest plot of salivary flow rate.

The first generation of electrostimulating devices was identified in the United States. It consisted of a probe applied between the dorsum of tongue and palate, delivering stimulated signals to sensitive neurons. The major advantage reported with this is that they did not produce any adverse effects. Recent advances in instrumentation led to the second and third generation electrostimulating device which was incorporated into an intraoral appliance and into osseo-integrated implants respectively. The osseo-integrated implants are placed in the region of lower molar tooth in close proximity to the lingual nerve which is stimulated to cause increase in saliva production.[13]

There are three different ways of activation of tissues with the use of TENS. These include conventional TENS, Acupuncture like TENS and intense TENS. Conventional TENS is the most commonly used method in dental practice. It used 10–200 pulses per second high frequency and low amplitude pulsed currents. This can be safely administered throughout the day with intermittent breaks to prevent skin irritation. On the contrary, acupuncture like TENS used low frequency (less than 10 pulses per second) and high amplitude and this can be used for about 30 min at a time. The intense TENS uses high frequency and high amplitude pulsed current which are just bearable to the patient. This is not used commonly. However specific details on the type of current to be used for xerostomia are still unknown.[15]

Compiling the available evidences on TENS for xerostomia, there was no statistically significant improvement in the salivary flow rate. However none of the studies reported any adverse effect as regards to TENS. Subjective assessment of xerostomia was reported only in one study. Overall there is limited evidence available to identify its utility. The major drawback identified was that most of the studies did not use specific type, amplitude and frequency of current. Hence a conclusion could not be drawn. Considering the advantage of not having any adverse effects, the utility of TENS could be investigated in future trials. More studies are required on patient or subjective assessment as well, which would still increase the possibility of using TENS as an alternative for symptomatic treatment of xerostomia. Also the type of TENS, the amplitude and frequency that will be required to produce improvement in xerostomic symptoms need to be studied in the future. The study is limited with a small total sample size and the co-relation of xerostomia with its different etiologies were not considered, due to limited available evidence. From our systematic analysis, we conclude that the current evidence does not support the use of TENS in the management of xerostomia and may be considered as a salivary substitute for symptomatic improvement.

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Conflict of interest

The authors do not have any conflict of interest.

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